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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,117	02/17/2004	Allen J. Borchardt	PC32031A	1196

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EXAMINER

OWENS, AMELIA A

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/783,117	Applicant(s) BORCHARDT ET AL.	
	Examiner Amelia A. Owens	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-37 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-37 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

1. Claims 1-37 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1,46,7,11,12,13,14-17,20,23-2933,35,37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. Finding a solvate is an empirical exercise. Determining if a compound will form a solvate is unpredictable. Physical properties can differ among solvates. The direction concerning the solvates is found @ page 20 lines 26-35. There is no working example of a solvate of a compound the formula I. The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of the claims as well as the presently unknown list of potential solvate derivatives embraced by the claim.

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MPEP 2164.01(a) states, “[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound of the claims form a solvate.

3. Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any physician skilled in the art of medicine, to make and/or use the invention commensurate in scope with these claims. The how to use requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. “The [eight] factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The main issues are the correlation between clinical efficacy for (1) increasing the bioavailability of a first compound metabolized by cytochrome P450; (2) inhibiting cytochrome P450 activity in a mammal; (3) inhibiting cytochrome P450 cytochrome P450 enzyme activity; (4) decreasing the metabolism in a mammal and Applicants' inhibition of P450 2D6 assay.

a) Determining if any particular claimed compound would cause any particular outcome - i.e. decrease metabolism, - would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different desired outcomes described below, or to testing them in an assay known to be correlated to clinical efficacy of such desired outcome. This is a large quantity of experimentation. b) The direction

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concerning (1) increasing the bioavailability of a first compound metabolized by cytochrome P450; (2) inhibiting cytochrome P450 activity in a mammal; (3) inhibiting cytochrome P450 cytochrome P450 enzyme activity; (4) decreasing the metabolism in a mammal is found @ page 19 lines 1-4, line 25 thru page 20 line 10, which merely states Applicants' intention to do so. Applicants describe formulations @ page 26 lines 10-24. Doses required to practice their invention are described @ page 26 line 25 thru page 27 line 4. Since none of the compounds has ever been used to cause any of the desired outcomes, how is the skilled physician to know what dose to use for each of these different outcomes? There are no guidelines for determining the doses needed to provide a increasing the bioavailability effect vs. a decreasing metabolism effect vs. an inhibiting P450 enzyme effect. Are the identical doses to be used for causing these unrelated outcomes? There is an assay described at page 82. However it is unclear how this assay is correlated to the desired outcomes. There is no working example of treatment of any of the outcomes – increase bioavailability/inhibit cytochrome P450 etc - in man or animals. The assay provides evidence that the present compounds were tested. Correlation to the desired outcome is not seen. “Correlation” as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. Is the state of the art such that a particular model used in the assay is recognized as correlating to - (1) increasing the bioavailability of a first compound metabolized by cytochrome P450; (2) inhibiting cytochrome P450 activity in a mammal; (3) inhibiting cytochrome P450 cytochrome P450 enzyme activity; (4) decreasing the metabolism in a mammal – as presently claimed. d) The nature of the invention is clinical treatment of disease with the claimed compounds, which involves physiological activity. e) The state of the clinical arts in cytochrome P450 is that there are several enzymes not just 2D6. See Rochat, Role of cytochrome P450 activity in the fate of anticancer agents and drug resistance: focus on tamoxifen, paclitaxel and imatinib metabolism, PMID: 15828850 (2005); Fuita, Cytochrome P450 and anticancer drugs, PMID: 16454691 (2006).

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved”, and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In

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cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the many compounds of the claims claim as well as the desired outcomes. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Certain Observations

4. USSN 11/204269 is noted. The application has a common inventor and a filing date of 8/15/2005 that is after the instant filing date, 2/17/2004. Further R2 is (CR⁶R⁷)_i(5-6membered heterocycle) instead of (CH₂)_n-X-Phenyl – thereby distinguishing the claims.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amelia A. Owens whose telephone number is 571-272-0690. The examiner can normally be reached on Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas C. McKenzie can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Amelia A. Owens
Primary Examiner
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